PATENT
0603-1003

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Philippe PEROVITCH et al. Conf. 1374

Application No. 10/588,005 Group 1615

Filed August 1, 2006 Examiner Aradhana Sasan

METHOD FOR THE DIFFUSION OF MOLECULES WHICH ARE INSOLUBLE IN AN AQUEOUS MEDIUM AND COMPOSITION USING SAID METHOD

DECLARATION UNDER RULE 132

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I Philippe PEROVITCH, Physician, hereby declare as follows:

I am one of the inventors of the above-identified U.S. patent application.

I am familiar with the present application, its prosecution before the United States Patent and Trademark Office, and the applied references of PANKHANIA et al. (WO 02/083119) and MITRA (WO 95/07103).

I personally designed and followed the controlled and randomized clinical trial versus placebo, dedicated to evaluate low dosage Ibuprofen lozenges' local effectiveness against mucous pain and inflammation, to reach a french New Drug Approval of the said application. The present invention relates to a method for

locally treating buccopharyngeal ailments in a subject. The method includes orally and locally administering a composition comprising a non-steroidal anti-inflammatory drug (NSAID) in a water-soluble amino acid salt form to the subject. The composition is then allowed to solubilize in the buccopharyngeal cavity of the subject, the composition being solubilized by the saliva of the subject. When solubilized, the amino acid dissociates from the NSAID and the now lipophilic NSAID can actively diffuse through the mucous tissues in the buccopharyngeal cavity of the subject without recrystallizing.

In order to demonstrate the patentability and unexpected results of the present invention, I am submitting the following observations and results.

Per-Mucous NSAID local delivery in Buccal / Pharyngeal ailments.

In 2008, as this local per-mucous technology was licensed and applied to treat acute pharyngitis through a clinical trial versus placebo, the Inventors were required by the licensee (Unither Pharmaceuticals Group), to try a stronger dosage of Ibuprofen Lysinate with 50 mg per unit, compared to the previous one which was only 25 mg Ibuprofen Lysinate per lozenge unit.

The clinical trial's first results on 60 patients with 25 mg Ibuprofen versus placebo were positive, and the next question was to evaluate whether these results could be improved by having a higher dosage of Ibuprofen. A 50 mg Ibuprofen Lysinate was thus specifiocally manufactured and tested to answer this requirement. Except for the dosage, all of the formulation elements were the same between the 25 mg and 50 mg formulations.

As detailed in the specification of the patent application, however, the formulation fails to adequately release and slowly dissolve the higher dosages, i.e., over 25 mg of Ibuprofen Lysinate. Indeed, when tested in the mouth, the 50 mg Ibuprofen Lysinate released a locally crystallized amount of Ibuprofen that could not be absorbed nor tolerated by the mucous.

Furthermore, although the formulation included strong peppermint flavoring, the taste led all the people involved in the testing to immediately stop sucking the medication, spit out the lozenge, and rinse their mouth. The Ibuprofen taste was determined to be "disgusting" and the taste continued for a long time.

These undesired side effects of the 50 mg Ibuprofen Lysinate were not present with the 25 mg dosage level.

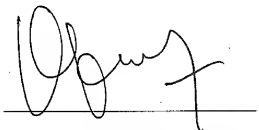
The clinical trial's conclusion was:
"This way, the UNITHER lozenges containing 14.63 mg of Ibuprofen have demonstrated a symptomatic activity, and with regards to the administered doses, even increase the safety margin in comparison with the oral forms. It could be a local, safer and preferable Ibuprofen Dose/Effect ratio in alternative to analgesic or anti-inflammatory oral / systemic treatments added to local emulcents".

Formula	A	B	C	Function
Ingredient				
IBUPROFEN LYSINATE	25.00 mg as *Ibuprofen base* =14.63 mg	50.00 mg as *Ibuprofen base* = 29.26 mg	75.00 mg as *Ibuprofen base* = 43.89 mg	Active ingredient
Liquid Peppermint Flavor IFF 15,06,1174	10.00 mg	10.00 mg	10.00 mg	Flavor
SORBITOL Type Neosorb P60W®	687.50 mg	662.50 mg	637.50 mg	Hygroscopic matrix
ASPARTAM	12.75 mg	12.75 mg	12.75 mg	Sweetener
Hydroxy Propyl Methyl cellulose	59.50 mg	59.50 mg	59.50 mg	Polymer gelling agent
Colloidal Anhydrous Silice Type Aerosil 200®	4.25 mg	4.25 mg	4.25 mg	Flowing agent
TALC	42.50 mg	42.50 mg	42.50 mg	Anti-adhesive
MAGNESIUM STEARATE (vegetal)	8.50 mg	8.50 mg	8.50 mg	Lubricant

Formulation's Total weight: 850 mg

Formula A: acceptable
Formula B: irritating, refused formula
Formula C: irritating, refused formula

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Philippe PEROVITCH, "Ibuprofen Lozenges Trial" Medical Manager.

Date July 7, 2010